UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,599	07/07/2003	David P. Andrew	09800080-0104	7759

23552 7590 02/02/2007

MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,599	ANDREW ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,38 and 42-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,38 and 42-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 13 November 2006 has been entered in full. Claims 1-18, 20-37, 39-41 are canceled. New claims 42-75 were added.

Claims 19, 38, 42-75 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The specification is in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations.

The objection to the drawings, as set forth at pages 5-7 of the previous Office Action (01 August 2006), is *withdrawn* in view of the amendment (13 November 2006).

The objection to claim 19, as set forth at page 7 of the previous Office Action (01 August 2006), is *withdrawn* in view of the amendment (13 November 2006).

The rejection to claim 19 under 35 U.S.C. 101, as set forth at pages 7-13 of the previous Office Action (01 August 2006), is *withdrawn*.

The rejection to claims 19 and 38 under 35 U.S.C. 112, second paragraph, as set forth at page 17 of the previous Office Action (01 August 2006), is *withdrawn* in view of the amendment (13 November 2006).

Claim Rejections - 35 USC § 112, First Paragraph

Claims 19, 38, 42-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification states that the instant invention (FCTRX, SEQ ID NO:6) has high homology to previously described S100/IcaBP-type calcium binding domains (page 9, lines 9-33). The specification states that serum concentrations of S100 cytokines according to the invention can be used as a marker for the clinical predictive value for metastatic tumors because the mouse gene fragment was originally identified in the tumors of Wnt-1 transgenic mice and human fragments used to produce the sequence were isolated from tumors (page 10, lines 7-20). Applicant cited various papers that link S100 proteins with malignancy.

The instant claims are not supported by an enabling disclosure for the following reasons. The specification fails to teach that the instant methods can be used for determining the presence of or predisposition to *all types of cancers* (claim 38). The specification teaches varied nucleic acid levels in only certain types of cancers. In addition, there are problems with using the tumor marker data for determining the presence or absence of cancer (claims 19, 38, and 61). In the instant examples, several tumor cell lines appeared to have high expression of nucleic acid encoding SEQ ID NO:6, **while other tumor cell lines of the same tissue** had low levels. There were

also high levels **of expression in the normal adjacent tissue (NAT) (sometimes higher than tumor cell lines of the same tissue)** (pages 87-88, 90-91). **Thus, it would not be clear to one skilled in the art, which samples are *statistically relevant.*** It is also not apparent if there were control tissues for every tumor cell line and tumor. Furthermore, it is known to those skilled in the art that tumor cell lines employed are not equal to tumor tissue. It is important to realize the key difference between tissue isolated from tumors and established cancer cell lines. Whereas it is true that all cancer cells (whether from tumors or established cell lines) are immortal, the cells from freshly isolated tumors are phenotypically the same as the tumor from which they were isolated, whereas cells in established cell lines have undergone numerous phenotypic changes. The cell culturing process alters gene expression and selects subgroups of cells, such that the cultured cells are no longer representative of the diseased tissue. The tumor cell lines were analyzed by polymerase chain reaction (PCR). Insignificant expression levels can be amplified until they appear significant. Barker et al. (Gynecologic Oncology 82, 57-63, 2001) teach that established cell lines may have undergone many manipulations that result in a loss of or acquisition of certain properties, resulting in the occasional lack of experimental reproducibility. More importantly, some cell lines do not possess the same receptors and markers as do counterpart neoplastic cells acquired from fresh, primary tumor. Baker et al. also teach that *in vitro* results acquired from these cell lines may not correlate with the results obtainable from patients (page 57). Anderson et al. (Clinical Immunology, Vol 102/1 Jan. pages 84-92, 2002) teach that *in vitro* culturing of established glioblastoma cell

lines lead to significant changes, which are known to affect the ability of immune cells to initiate an anti-tumor response. Anderson et al. teach that late passage cell cultures no longer represent the original tumor because of drifting of the initial culture *in vitro* to a heteroclonal population (page 84-85 and 89-92). The instant specification fails to teach a correlation between nucleic acids encoding SEQ ID NO:3 or SEQ ID NO:6 and the presence of cancer because of the inconsistent expression levels of nucleic acid molecules and because it is unclear if the nucleic acid levels would be enhanced or decreased compared to a normal control tissue.

Claim 59 recites, "wherein the inflammation or cancer associated with altered levels of the nucleic acid are diseases or disorders associated with cell hyperproliferation and/or loss of cell proliferation". The specification, however does not teach functional characteristics/mechanisms of action of FCTRX. Therefore, it is unclear how FCTRX functions. The references submitted by Applicant teach various biological functions for S100 proteins (purported homolog of FCTRX) and not all of the S100 proteins have a known mechanism.

The instant claims are not supported by an enabling disclosure because the specification fails to teach that the instant methods can be used for determining the presence of inflammation (claims 19, 38). The specification states that S100 proteins have been implicated in inflammation (page 10, line 33-page 11, line 10). The specification states that FCTRX can be used to modulate FCTRX activity to treat inflammation (page 44, lines 5-15; page 72, lines 3-11, pages 78, lines 7-13 and page 82, lines 25-34). The examples teach the incubation of small airway epithelium cells

with cytokine TNF-alpha (page 92, lines 13-23). The specification states that expression of clone 65677221-3-frag (nucleic acid encoding SEQ ID NO:6) is increased by TNF-alpha in epithelial airways. The specification concludes that inflammatory conditions can be treated or prevented by antagonizing expression or activity of FCTRX nucleic acids or polypeptides, respectively (page 97). The data is not persuasive because it only demonstrates that when small airway epithelium cells are incubated with TNF-alpha, nucleic acids encoding SEQ ID NO:6 are expressed; such is not tantamount to indicating the presence of inflammation. TNF-alpha is a multifunctional cytokine which exerts a myriad of diverse biological actions such as adiopocyte metabolism, liver injury, insulin resistance in adipocyte tissue, and apoptosis (please see submitted references). Thus, induced expression of a nucleic acid molecule alone, does not teach its significance. For example, Lackmann et al. (The Journal of Immunology, Vol. 150/7 pages 2981-2991, 1993) identify the S100 protein, CP-10, as a cytokine involved in inflammation. Lackmann et al. teach chemotactic activity of polymorphonuclear cells in the presence of CP-10 (abstract and Figures 3-4). Lackmann et al. teach that CP-10 elicited inflammatory infiltration in a skin test (abstract and Figure 5).

Additionally, claim 38 recites the limitation, "method for determining the predisposition to inflammation or cancer". The specification fails to teach via examples, working models or submit literature that provides guidance to discerning what level of nucleic acid encoding SEQ ID NO:3 or SEQ ID NO:6 would be predictive of a predisposition to cancer or inflammation. The instant specification teaches levels of

nucleic acids encoding SEQ ID NO:6. What sample levels would demonstrate that a subject is predisposed to cancer or inflammation?

The instant data is preliminary at best. The instant specification fails to teach a correlation between nucleic acids encoding SEQ ID NO:3 or SEQ ID NO:6 and the instant claims. Further research would be required to establish whether the instant invention can be used as diagnostic marker.

Lastly, the instant claims are not supported by an enabling disclosure because of the limitation "nucleic acid molecule encoding a polypeptide having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:6". Applicant cites case law and the legal standards for enablement. Applicant argues that is well accepted that nucleic acid sequences having less than full identity may be detected through simple hybridization methods and nucleic acid probes for such detection are readily predicted and produced. Applicant contends that structural information has been provided as well as multiple comparisons to the human ortholog (SEQ ID NO:6) and S100 family members. Applicant directs the Examiner's attention to page 9 and Figures 4B-4E. Applicant contends that the specification teaches that amino acids shaded in grey can be mutated to a residue with comparable steric and/or chemical properties without altering protein structure or function.

Applicant's arguments have been fully considered but are not considered persuasive. Contrary to Applicant's assertion, the data fails to establish a relationship between expression of a nucleic acid encoding a polypeptide having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:6 ***and*** upregulation of

expression in tumor cells. There is no disclosure of any variants that are encoded by nucleic acids, which are overexpressed in any tumor cells. Furthermore, the art does not recognize employing a variant polynucleotide for the purpose of screening/diagnosis of a disease or condition. A variant probe is less specific for its target. The purported utility is that the polynucleotides are useful in that they have a particular biological activity (i.e. enhanced expression of the nucleic acid is indicative of cancer of inflammation). The instant nucleic acid allows imperfect matches and carry the risk of obtaining false signals from unrelated DNA sequences. There is no guidance (or working examples) regarding what changes can be made without loss of probe specificity. Applicant's arguments regarding amino acid sequence and structure comparison of SEQ ID NO:6 are not found persuasive because the claim limitation "wherein enhanced expression of the nucleic acid is indicative of cancer or inflammation" is a feature of the nucleic acid ***not*** the amino acid.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

Claims 19, 38, 42-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant cites case law. Applicant states that the sequence and thereby the complete chemical structure of the polypeptides of SEQ ID NOs:3 and 6 are provided. Applicant contends that structural information has been provided as well as multiple comparisons to the human ortholog (SEQ ID NO:6), calcium binding proteins and S100 family members. Applicant directs the Examiner's attention to page 9 and Figures 4B-4E. Applicant contends that there is sufficient recitation of distinguishing identifying characteristics to define the envisioned polypeptides.

Applicant's arguments have been fully considered but are not considered persuasive. As was stated in the previous Office Action, the specification provides adequate written description for nucleic acids encoding SEQ ID NO:6, but not variants thereof. Applicant's arguments regarding amino acid sequence and structure comparison of SEQ ID NO:6 are not found persuasive because the claim limitation "wherein enhanced expression of the nucleic acid is indicative of cancer or inflammation" is a feature of the nucleic acid . Applicant cites pages which discuss very broad nucleic acid changes in FCTRX. Specific, not general guidance is what is needed. There is no disclosure of any variants that are encoded by nucleic acids that are overexpressed in any tumor cells. The disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is variant, polynucleotides encoding SEQ ID NO:6, alone is insufficient to describe the genus. The disclosure fails to provide a representative number of species to describe the genus. A single species (i.e. nucleic acid molecule encoding SEQ ID NO:6) is not representative of the claimed genus.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTION/OBJECTIONS

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 19, 42-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite because the preamble does not agree with the intended use. The body of the claim **(wherein enhanced expression of the nucleic acid molecule is indicative of cancer or inflammation)** and the preamble **(a method for determining the presence or absence of the nucleic acid)** is not consistent, thus the metes and bounds of the instant claim cannot be determined.

Claim 19 is also indefinite because of the recitation, "a method for **determining the presence or absence** of the nucleic acid encoding a polypeptide..." "**wherein enhanced** expression of the nucleic acid molecule is indicative...". The metes and bounds of the instant claim cannot be determined because it is unclear what the enhanced expression is being compared to.

Claim Objections

Claims 19, 38 and 59 are objected to because of the following informalities: The instant claims are not limited to the elected invention. Appropriate correction is required.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
1/23/07

MARIANNE P. ALLEN
PRIMARY EXAMINER

AU1647 2/1/07